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(19) (CA) # CANADIAN PATENT

(54) PREPARATION OF A HYPOCHOLESTEROLEMIC

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A B S T R A C T

A method for the preparation of 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl) acetate which comprises treating 2-acetamidoethyl (4-chlorophenyl)-haloacetate with 3-trifluoromethylphenol or with a salt of 3-trifluoromethylphenol. The 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)-acetate thus obtained is a hypocholesterolemic and hypolipemic agent which effectively reduces the concentration of cholesterol, triglycerides and other lipids in blood serum.

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This invention relates to a novel method for the preparation of 2-acetamidoethyl (3-trifluoromethyl-phenoxy) (4-chlorophenyl)acetate.

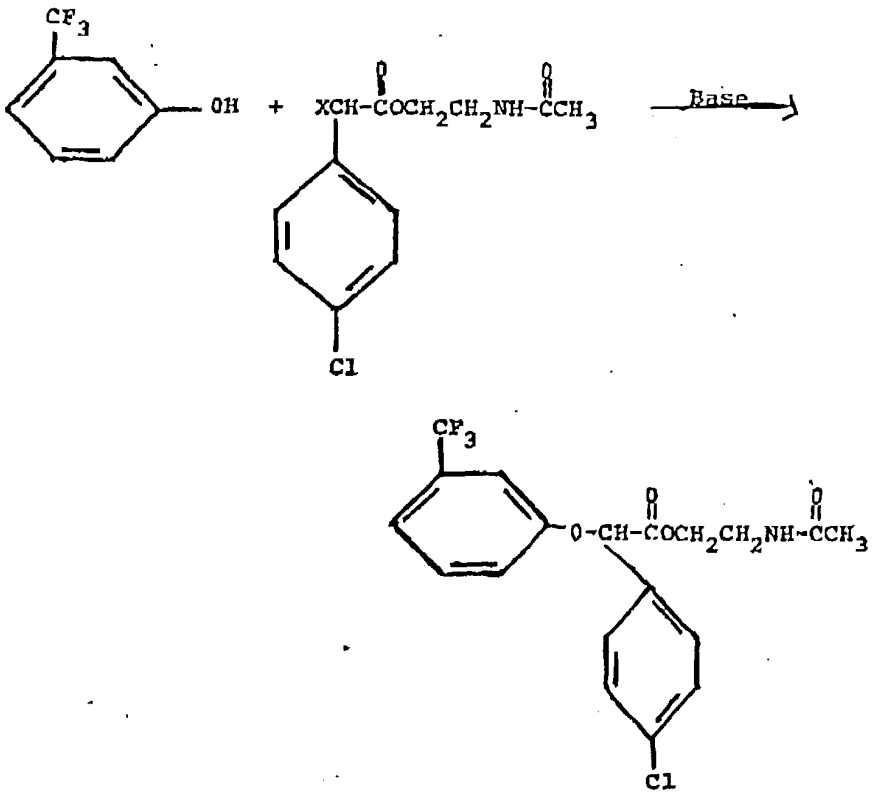
There is no clear agreement about the actual role of cholesterol and triglycerides in the localization of atherosclerotic plaques but numerous studies support the concept that cholesterol and triglycerides play a major role in the pathogensis of atherosclerosis because along with other lipids and fibrin they accumulate in the arterial intima and subintima and produce arterial corrosion.

It is the purpose of this invention to describe a novel method for the preparation of 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate which product has proved effective in reducing the concentration of cholesterol, triglycerides and other lipids in blood serum. This compound induces a significant reduction in

cholesterol and triglyceride levels in serum and it achieves this result with little or no irritation to the gastrointestinal tract.

According to this invention 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate is obtained by treating 2-acetamidoethyl (4-chlorophenyl)-haloacetate with 3-trifluoromethylphenol or with a suitable salt of 3-trifluoromethylphenol. Suitable salts include those obtained by treating 3-trifluoromethylphenol with any organic or inorganic compound having a pH equal to or greater than 7. Typical of these are salts derived from the following basic reagents: the alkali metal or alkaline earth metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and the like, alkaline metal or alkaline earth metal carbonates or bicarbonates such as sodium carbonate, potassium carbonate, calcium carbonate, sodium bicarbonate potassium bicarbonate, and the like, basic metal oxides such as sodium oxide, potassium oxide, calcium oxide, cadmium oxide, gold oxide, silver oxide, and the like, tertiary organic bases, for example, tertiary alkylamines such as trimethylamine, triethylamine, pyridine, and the like, quaternary ammonium bases, for example, tri-lower alkylammonium alkoxides such as trimethylammonium methoxide, triethylammonium ethoxide, and the like or alkali metal or alkaline earth metal alkoxides such as sodium methoxide, sodium ethoxide, potassium ethoxide, potassium tertiary-butoxide and the like. Alternatively,

in lieu of a salt of 3-trifluoromethylphenol as the reactant, the said phenol may be employed per se in the process. However, in practice, when 3-trifluoromethylphenol is employed it is usually advantageous to conduct the reaction in the presence of a base. The use of a basic reagent is not critical to the process but, in general, it does serve to promote the reaction and increase the product yield. The following equation illustrates this method of preparation, i.e., using 3-trifluoromethylphenol in the presence of base, however, it is to be understood that any salt of 3-trifluoromethylphenol, such as those defined above, or simply 3-trifluoromethylphenol per se may also be employed in otherwise similar process to afford an identical product (I):



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wherein X is halo, for example, chloro, bromo, fluoro or iodo, and the like and the basic reagent (i.e., "Base") is any organic or inorganic compound having a pH equal to or greater than 7. Thus, suitable bases include, for example, any alkali metal or alkaline earth metal alkoxide, carbonate, bicarbonate or hydroxide such as sodium methoxide, potassium methoxide, calcium ethoxide, sodium ethoxide, sodium carbonate, potassium carbonate, calcium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide or calcium hydroxide, any suitable tertiary amine, for example, a trialkylamine such as trimethylamine, triethylamine and the like, an heterocyclic amine such as pyridine or quinoline and the like, basic metal oxides such as sodium oxide, potassium oxide, calcium oxide, cadmium oxide, gold oxide, silver oxide and the like or quaternary ammonium bases, for example, tri-lower alkylammonium alkoxides such as trimethylammonium methoxide, triethyl-ammonium ethoxide and the like.

The choice of a solvent is not critical to the reaction and, in general, the process may be conducted in any suitably inert medium in which the reactants are reasonably soluble. Suitable solvents include for example, tetrahydrofuran, methylene chloride or hydrocarbons of the aliphatic, acyclic and aromatic variety which are pentane, hexane, decane, dodecane, cyclohexane, benzene, toluene, xylene and the like or alkanols, for

example, lower alkanols such as methanol, ethanol and the like. However, the synthesis does proceed most advantageously in hydrocarbons of the type described above and, therefore, the use of such media constitutes a preferred embodiment of this invention. Also the process may be conducted at ambient temperatures but, in practice, the reaction is facilitated by the application of heat. In general, it is most desirable to employ temperatures in the range of from about 40°C. up to the reflux temperature of the reaction mixture over an extended period of from about one to twenty hours.

The 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate product of this invention is a crystalline solid which may be purified by recrystallization from a suitable solvent or from a mixture of solvents as, for example, by recrystallization from a lower alkanol such as methanol, ethanol or isopropanol and the like or from a mixture of said alkanols.

The 2-acetamidoethyl (4-chlorophenyl)haloacetate, halide employed as the starting material in the process of this invention is obtained by treating 4-chlorophenylacetic acid (II, infra) with an halogenating agent to afford the corresponding 4-chlorophenylacetyl halide intermediate, which intermediate is then treated with a second halogenating agent capable of substituting halogen for hydrogen on the alpha carbon of the acid halide nucleus. The (4-chlorophenyl)haloacetyl halide thus obtained is then treated with 2-acetamidoethanol in the

presence of a base such as pyridine or sodium carbonate to yield the desired 2-acetamidoethyl (4-chlorophenyl)-haloacetate. In this synthesis the initial halogenation step, which results in the conversion of 4-chlorophenyl-acetic acid (II) to its acid halide, may be carried out with any reagent capable of converting carboxylic acids to their corresponding acid halides. Suitable reagents thus include, for example, the thionyl halides such as thionyl chloride, thionyl bromide and the like. The 4-chlorophenylacetyl halide thus obtained may then be isolated and purified or, as generally occurs in practice, the said 4-chlorophenylacetyl halide intermediate is allowed to remain in solution and the reaction mixture is treated with a second halogenating agent capable of converting the said acid halide to the desired (4-chloro-phenyl) haloacetyl halide intermediate. Suitable halogenating agents which may be used in this step include, for example, bromine and chlorine and the like. The following equation, wherein the halogenating agents employed are thionyl chloride and gaseous bromine, respectively, illustrate this method of preparation; however, it is to be understood that any other functionally equivalent reagents may be substituted therefor in an otherwise similar process to afford an identical compound:

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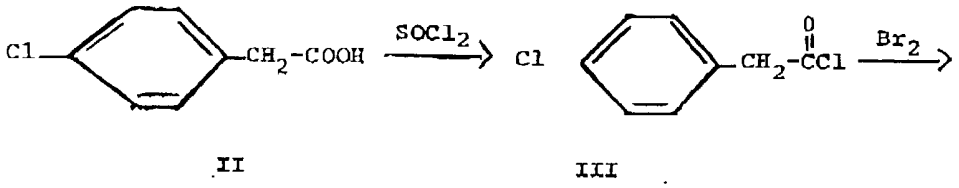
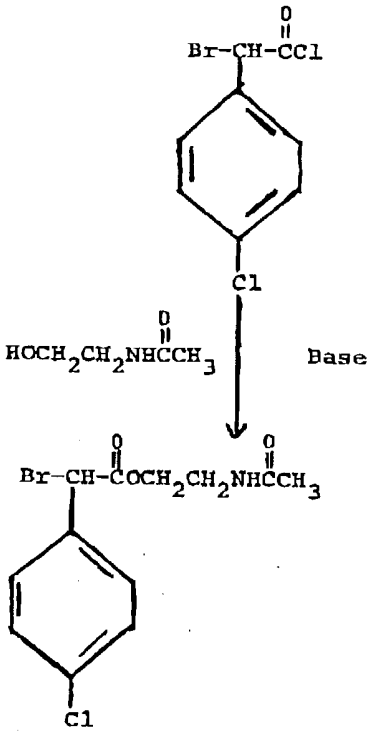


II III



1 The following examples illustrate the process
2 of this invention. However, the examples are illustrative
3 only and this invention should not be construed as being
4 limited thereto since other reaction conditions and other
5 functionally equivalent reagents may be substituted there-
6 for to afford an identical 2-acetamidoethyl (3-trifluoro-
7 methylphenoxy) (4-chlorophenyl)acetate product.

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EXAMPLE 1

2-Acetamidoethyl (3-Trifluoromethylphenoxy) (4-Chlorophenyl)acetate

Step A: (4-Chlorophenyl)bromoacetyl Chloride

4- Chlorophenylacetic acid (170 g., 1.0 mole) and thionyl chloride (150 g., 1.25 mole) are placed in a 2-liter flask fitted with a stirrer, reflux condenser and dropping funnel. The mixture is stirred and heated at reflux for two hours with stirring while bromine (160 g., 1.0 mole) is added from the dropping funnel over a three-hour period. Heating under reflux is continued for 20 hours. The volatiles are then removed at the aspirator and dry benzene (500 ml.) is added and evaporated in vacuo. The 2.68 g. of (4-chlorophenyl)-bromoacetyl chloride thus obtained is in the form of a brown oil.

Step B: 2-Acetamidoethyl (4-Chlorophenyl)-bromoacetate

A solution of (4-chlorophenyl)bromoacetyl chloride (268 g., 1.0 mole) in 415 ml. of ether is added to a mixture of 2-acetamidoethanol (103 g., 1.0 mole), dimethylformamide (1164 ml.) and pyridine (90 ml.) at 5°C. over a 30-minute period. The reaction mixture is stirred and protected from atmospheric moisture during the addition. After stirring an additional hour at 5°C., the reaction mixture is warmed to room temperature and allowed to stand for 16 hours. Water (2 liters) and ether (1.66 liters) are added and the resulting aqueous

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layer is separated and extracted twice with 1.66 liters of ether. The ether extracts are then combined and dried over sodium sulfate. The ethereal solution is concentrated, flushed with ether and the concentrate is diluted with 200 ml. of methanol. The methanolic solution of 2-acetamidoethyl (4-chlorophenyl)bromo-acetate thus obtained is used directly in the next step.

Step C: 2-Acetamidoethyl (3-Trifluoromethyl-phenoxy) (4-Chlorophenyl)acetate

3-Trifluoromethylphenol (163.2 g., 1.0 mole) in 200 ml. of benzene is added to a mixture of 1.0 mole of sodium methoxide in 1 liter of benzene. To this mixture is added a solution of 2-acetamidoethyl (4-chlorophenyl)bromoacetate (334.5 g., 1.0 mole) in 200 ml. of benzene. The reaction is heated under reflux for 15 hours and then concentrated in vacuo. Ether (4.0 liters) and water (1.2 liters) are added to the residue and the organic layer is separated, washed with dilute sodium hydroxide and water and then dried over sodium sulfate. The benzene solution is concentrated to yield 382 g. of crystalline residue, m.p. 82-89°C. Re-crystallization from isopropanol yields 254 g. of 2-acet-amidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)-acetate, m.p. 93.5-95.5°C.

Upon substitution an equilmolar amount of the sodium salt of 3-trifluoromethylphenol and benzene (200 ml.) for the 3-trifluoromethylphenol reactant and method of Example 1, Step C and following the procedure described

therein there is thus obtained 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate. Recrystallization from ethanol affords substantially pure 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate, m.p. 92-94°C.

EXAMPLE 2

2-Acetamidoethyl (3-Trifluoromethylphenoxy) (4-Chlorophenyl)-acetate

Step A: 4-Chlorophenylacetyl Chloride and (4-Chlorophenyl)bromoacetyl Chloride

Thionyl chloride (13.0 g., 0.117 mole) was added to 4-chlorophenylacetic acid (17.06 g., 0.1 mole) and the resulting mixture was stirred and brought to boiling. The mixture was then boiled under reflux for one-half hour and cooled to afford a solution of 4-chlorophenylacetyl chloride.

Bromine (20.0 g., 0.125 mole) was added to the cooled solution of 4-chlorophenylacetyl chloride and the resulting mixture was protected from moisture and heated at 105°C. under reflux for three hours. The resulting mixture was then subjected briefly to vacuum distillation to remove low boiling fractions and three 10 cc. portions of benzene were added and the mixture was distilled at atmospheric pressure to afford (4-chlorophenyl)bromoacetyl chloride.

Step B: 2-Acetamidoethyl (4-Chlorophenyl)-bromoacetate

The crude (4-chlorophenyl)bromoacetyl chloride obtained in Step A was dissolved in benzene (100 cc.) and to this mixture was added 11.0 g. of dried anhydrous

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sodium carbonate. Ten portions of 2-acetamidoethanol (10.3 g., 0.1 mole) was then added with stirring and cooling to moderate the resulting midly exothermic reaction. Within 15 minutes after the addition of the last portion of 2-acetamidoethanol the esterification was complete. The 2-acetamidoethyl (4-chlorophenyl)-bromoacetate thus obtained was used directly in the next step.

Step C: 2-Acetamidoethyl (3-Trifluoromethylphenoxy) (4-Chlorophenyl)acetate

The solution of 2-acetamidoethyl (4-chlorophenyl)-bromoacetate from Step B was transferred to a separatory funnel and washed with two 100 cc. portions of water. The flask was then rinsed into the separatory funnel with a mixture of water (10 cc.) and benzene (10 cc.) and left wet. To this solution was added, with stirring, sodium carbonate (11.0 g.) followed by the addition of 3-trifluoromethylphenol (16.2 g.). The resulting mixture was heated at reflux for twenty hours and then cooled and extracted with water (100 cc.), ice cold 0.5 N sodium hydroxide (100 cc.), 3% sodium bicarbonate (100 cc.) and 1% sodium chloride (100 cc.). The mixture was then stirred briefly with sodium sulfate (10.0 g.), activated decolorizing charcoal (1.0 g.) was added and the resulting mixture was filtered and subjected to vacuum distillation to remove benzene. The mixture was then flushed with two 50 cc. portions of methylcyclohexane to afford 78% crude 2-acetamidoethyl (3-trifluoromethylphenoxy)

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(4-chlorophenyl)acetate (32.4 g., 0.078 mole) which partially crystallized on standing. Crystallization of the crude product from isopropanol (36 cc.) yielded a 79% recrystallization recovery of 2-acetamidoethyl (3-trifluoromethylphenoxy) (4-chlorophenyl)acetate (25.6 g., 0.0617 mole), m.p. 92-94°C.

Any departure from the above description which conforms to the present invention is intended to be included within the scope of the claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for the preparation of 2-acetamidoethyl-(3-trifluoromethylphenoxy)(4-chlorophenyl)acetate which comprises treating 2-acetamidoethyl(4-chlorophenyl)haloacetate with 3-trifluoromethylphenol in the presence of a base or with a salt of 3-trifluoromethylphenol.

2. The method according to Claim 1 wherein 2-acetamidoethyl(4-chlorophenyl)bromoacetate is treated with 3-trifluoromethylphenol in the presence of a base.

3. The method according to Claim 2 wherein the base is derived from an alkali metal or alkaline earth metal.

4. The method according to Claim 3 wherein the base is an alkali metal alkoxide, alkali metal carbonate, alkali metal hydroxide or alkali metal bicarbonate.

5. The method according to Claim 1 wherein 2-acetamidoethyl(4-chlorophenyl)haloacetate is treated with 3-trifluoromethylphenol in a hydrocarbon solvent and in the presence of a base selected from alkali metal alkoxide or alkali metal carbonate, at a temperature of from about 40°C. up to the reflux temperature of the reaction mixture.

6. The method according to Claim 5 wherein the base is sodium carbonate.

7. The method according to Claim 5 wherein the hydrocarbon solvent is benzene.

8. The method according to Claim 5 wherein the temperature employed is the reflux temperature of the reaction mixture.

9. The method according to Claim 1 wherein 2-acetamidoethyl(4-chlorophenyl)bromoacetate is treated with a salt of 3-trifluoromethylphenol.

10. The method according to Claim 9 wherein the salt of 3-trifluoromethylphenol is an alkali metal or alkaline earth metal salt.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente